UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/976,886	11/24/97	RIMM D	H-1296

HM22/0331

WILLIAM W JONES
6 JUNIPER LANE
MADISON CT 06443

EXAMINER	
EYLER, Y	
ART UNIT	**PAPER NUMBER**
1642	6

DATE MAILED: 03/31/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/976,886	Applicant(s) Rimm et al.
	Examiner Yvonne Eyler	Group Art Unit 1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-14* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-14 are pending and under consideration in the application.

Specification

1. The use of the trademark QBC has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

2. Claims 1-14 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The reference to "abnormal" cells is not clear in the claims as there is no definitive description of what constitutes normal and what constitutes abnormal. The specification discloses only the detection of epithelial cells indicative of cancer cells or hematologic progenitor cells in a whole blood sample which are therefore assumed to constitute abnormal cells. No other "abnormal" cells are described or detected and it is not clear what it encompassed as "abnormal."

The term "well-defined zone" or "well-defined annular zone" found generally in the claims is unclear because the metes and bound of the specified zone cannot be determined. There are no identifying characteristics of the zone supplied so that one of skill knows the properties that facilitate identification of the zone. The recitation that the zone is formed by various embodiments of an insert does not clarify the language.

The terms epitopic-specific labeling agents which differentiate abnormal target cells and epitopic labeling materials which differentiate cancer cells from other cells and other renditions of the language using "highlight" or "signal result" found generally in the claims is vague and indefinite because the metes and bounds of the agents and materials cannot be determined. Identifiable, measurable, definitive characteristics are not provided. Further, it would appear that the agents and materials bind to the cells and label the cells but do not literally differentiate or separate the cells from one another. The specification discloses only antibodies specific for epithelial-specific epitopes or HPC-specific epitopes, which epitopes are absent on normal epithelial cells and non-precursor blood cells which facilitate distinction between the types of cells by preferential labeling. No other agents are disclosed or the parameters and characteristics of such agents taught.

The terms stains or colorants that clarify cell morphology and cell morphology clarifying stains are vague and indefinite because it is not clear what the identifying characteristics of the stains and colorants are nor can the metes and bounds of the compounds encompassed be determined. It is not clear what measurable difference is classified as a clarified morphology and

what type of compounds facilitates this clarification. Further, it is not clear what defines an "abnormal morphology" and what defines and "normal morphology" and how this is used to enable detection of target cells, cancer cells, epithelial cells, or hematological precursor cells. This applies specifically to claims 1, 2, 3, 6, 8, 13, and 14.

The use of the term "differentiate" in steps b, e, and f in Claim 1 is confusing. The combination with labeling agents does not directly differentiate the abnormal cells, rather it labels them so that they may be more easily distinguished from non-labeled, normal cells. Further confusion is introduced in steps e and f with the recitation that differentiated cells are enumerated and examined, because technically the antecedent basis is incorrect since the cells of step b haven't been differentiated yet. Additionally, "differentiated cells" has a more common biological meaning of cells in a developmental pathway and confuses the issue of wether differentiated blood cells are enumerated from premature blood cells. This could be clarified by using terminology such as "labeled" in place of differentiated.

Further, the preamble states that target abnormal nucleated cells are detected, but the correlation steps don't actually resolve how they are detected, rather they only refer to enumerating and examining differentiated cells. Addition of language to indicate that enumeration of the "differentiated" cells is equivalent to enumerating the target cells is needed. Finally, it is not clear what the cells are morphologically examined for and how morphology correlates with detection of target abnormal nucleated cells.

Claims 2 and 14 do not specify when the blood sample is centrifuged and are confusing, because the language could encompass a blood sample that is first centrifuged and then placed in the tube. It's also not clear when the blood sample is combined with labeling agents and colorants.

The steps of claim 2 recite that a percentage of all labeled cells which are disposed in said well-defined annular zone is identified, but there is no clear description of what percentage or percentage of what is identified nor is it clear how identification of an unknown percentage facilitates detection of target abnormal nucleated cells. Claim 2 further recites that morphology of the unknown percentage is examined to identify any cells that display abnormal morphology, but the metes and bounds of abnormal morphology are not established and neither is the correlation between an "abnormal" morphology and detection of target abnormal cells delineated.

Claim 3, similar to claim 2, is not clear as to when labeling agents and colorants are added to the sample in the tube. Further, the claim recites a well-defined zone to which platelets have gravitated but does not describe where or how this zone is identified. Finally, the correlation step recites enumerating morphologically abnormal epithelial cells which have gravitated to the zone, but does not recite how enumeration of morphologically abnormal epithelial cells facilitates enumeration of circulating epithelial cells in general. Further, there is no description of the identifiable morphological attributes that identify an epithelial cell as abnormal.

Claim 4 refers to the constituent components of blood, which is vague and indefinite because it is not clear what is encompassed by the term. Does this indicate separation of NaCl for

water from other chemicals and molecules, for example. Clarification that the cellular components of the blood sample are separated is suggested. This also applies to claims 5 and 6.

Claims 4, 5, and 6 are vague and indefinite in the recitation of an "insert that is operable", because while one of skill would be able to determine if an insert were generally cylindrical, the metes and bounds of an insert defined only in that it is operable to form a well-defined zone, which zone is not identified or characterized and is itself vague and indefinite as discussed above, cannot be determined. There are no identifiable characteristics of the claimed insert which allow one to determine if an insert meets the claim language.

Note that claims 4, 5, and 6 recite the same method steps, but the centrifugation of claim 4 results in selective accumulation of only nucleated cells which are not conventional blood cells into the zone while the centrifugation of claim 5 results in accumulation of any nucleated cells into the zone, and the centrifugation of claim 6 results in the exclusion of blood cells from the zone. However, there is no distinguishing description between these centrifugations with different results to allow one of skill in the art to identify the parameters of the centrifugations which result in such drastically different separations. Similarly, the centrifugation of claims 9 and 13 appears to result in only abnormally nucleated cells migration to the zone.

Similar to claim 1, the examination of "differentiated" cells in the zone as claimed in claims 4, 5 , 6, 13 is confusing given the unclear meaning of "differentiated." There is also no descriptive correlation between the examination of the cells and the determination that they are cancer or hematologic progenitor cells or any other cells.

Claim 7 refers to the insert as an axially elongated insert but does not specify what axis is elongated nor any other identifying features of the insert, nor does the claim indicate the indefinite zone is formed by the insert. Thus, as discussed above, the examination of a well-defined zone is not clear, since the identifiable parameters of the zone are not clear. The identification of epithelial cells by labeling is clear, however, the role that the centrifugation and zone plays in the identification of this claim is not clear and appears to be more directly related to the separation of epithelial cells.

Similar to claim 7, claim 9 refers to an axially elongated insert but does not specify what axis is elongated. The claim recites that the tube and insert form a well-defined zone, but as discussed supra, does not provide definitive characteristics of the zone to facilitate identification. Claim 7 shares the above identified indefiniteness of epitope-specific agents that differentiate, but these agents further "highlight" the difference and characteristics of which cannot be determined, thus leading to further confusion regarding the metes and bounds of the agents and the identification of agents that meet the claim language. Also, similar to claim 1, claim 9 recites the enumeration of labeled cells and the examination of morphology but does not include how these parameters facilitate detection of target abnormal nucleated cells.

Claim 10 is vague and indefinite because it is not clear what a microscopical instrument is. Is this a microscope or an extremely tiny instrument of some sort?

Claim 11 is further vague and indefinite because the metes and bounds of "a predetermined power" cannot be determined. It cannot be determined what powers this encompasses.

Claim 13 is vague and indefinite because, like claims 7 and 9, it refers to an axially elongated insert but does not specify what axis is elongated or characterize the insert in any other identifiable way. Similar to claim 1, claim 12 also fails to provide a clear correlation step explaining how enumeration of "differentiated" cells and examination of morphology facilitates detection of target abnormal nucleated cells.

The description of the signal result in claim 14 is confusing. The result is defined as present or not and defined by the presence or absence of one or more undefined epitopes on target cells. The signal is not, however, actually defined by the epitopes, rather it is indicative of the presence of the epitopes. Claim 14 also recites identification by morphology of target cells but does not describe the definitive morphology of the target cells in such a way as one of skill would be able to determine the metes and bounds of the morphology of target cells.

For the reasons given above, the invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same. One of skill in the art would not be enabled to make or identify a tube with a well-defined zone as required by the methods because the identifiable characteristics of the tube which would enable one of skill in the art to reproduce it or identify it are not set forth in a full, clear, concise manner. Further, one of skill would not be enabled to add the agents and colorants to the blood sample commensurate in

scope with the claimed method because the metes and bounds of the agents and colorants cannot be determined. There is insufficient description of the agents and colorants to enable one of skill in the art to make or identify them for combination with the blood sample. One of skill in the art would also not be enabled to perform the centrifugation required to dispose the various sets of cells into the "well defined zone" because the centrifugations appear to result in several different types of separations yet the parameters such as time, G-force, etc. that facilitate the different results are not provided and it would require undue experimentation by one of skill to determine the parameters that result in the different separations as claimed. Finally, the methods recite examination of morphology and enumeration of "differentiated" cells, but one of skill in the art, absent further guidance regarding the characteristics examined and predictably correlated with the various types of "abnormal" target cells would not be enabled to identify the target cells.

The applicant is reminded that amendments should point to a basis in the specification so as not to add any new matter.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

(f) he did not himself invent the subject matter sought to be patented.

4. Claims 1, 2, 5, 6, 9, 10, 13 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Levine et al. (U.S. # 5,834,217) under 35 U.S.C. 102(a and e) as being anticipated by Levine et al. (U.S. # 5,635,362).

Both Levine et al. ('217 and '362) disclose the detection of the presence or absence of analytes using the instant methods of transparent tubes with bores and labeling of the analytes with agents and addition of colorants to clarify. The analytes detected are taught to include nucleated cells, including hematopoietic progenitors and other lymphocytic nucleated cells, the morphology of which is clarified by the colorant. See columns 7-10 and the abstract.

5. Claims 1, 2, 5, 6, 9, 10, 13, 14 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The inventive entities of Levine et al. (U.S. # 5,834,217 and 5,635,362) differ from the instant inventive entity, yet '217 and '362 disclose the detection of the presence or absence of analytes using the instant methods of transparent tubes with bores and labeling of the analytes with agents and addition of colorants to clarify. The analytes detected are taught to include nucleated cells, including hematopoietic progenitors and other lymphocytic nucleated cells, the morphology of which is clarified by the colorant. See columns 7-10 and the abstract.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-10, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levine et al. (U.S. # 5,834,217) or Levine et al. (U.S. # 5,635,362) as applied to claims 1, 2, 5, 6, 9, 10, 13, and 14 above and in view of Nagy (J Exfoliative Cytology, 123-133, 1965-IDS).

Levine et al. ('217 and '362) do not specify that the nucleated cell analyte detected be epithelial or cancer cells. However, Nagy teach the art-known phenomenon that cancer cells (which are epithelial) are found in the white cell layer of whole blood and further teach the morphological identification of the cells.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to extend the methods of Levine et al. ('217 or '362) to the detection any nucleated cell, including epithelial and cancer cells with a reasonable expectation of success given the knowledge that cancer cells are present in the same layer of the blood as that measured by Levine et al and one would be motivated to do so in order to detect cancer for clinical implications.

8. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levine et al. (U.S. # 5,834,217) or Levine et al. (U.S. # 5,635,362) as applied to claims 1, 2, 5, 6, 9, 10, 13, and 14 above and in view of Wardlaw (U.S. # 4,156,570).

Levine et al. ('217 and 362) teach as set forth above but do not specify the use of a microscopical instrument which measures a thickness equal to the focal operating range of 10-100 microns.

Wardlow teaches, however, the use of a microscopical instrument that measures the transverse section of 10-100 microns of the instant tubes to minimize the degree of error. See column 1.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to measure the tubes of Levine et al. ('217 and '362) using the microscopical analysis of Wardlaw. with a reasonable expectation of success to minimize the degree of error as taught by Wardlaw.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5, 6, 9, 10, 13, and 14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 5,834,217. Although the conflicting claims are not identical, they are not patentably distinct from each other because the analyte measured the claimed method of '217 may be nucleated cells as instantly claimed.

Claims 3, 4, 7, and 8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 5,834,217 as applied to claims 1, 2, 5, 6, 9, 10, 13, and 14 above in view of Nagy (J Exfoliative Cytology, 123-133, 1965-IDS).

The claimed invention of '217 is not specifically drawn to the detection of epithelial or cancer cells. However, Nagy teach the art-known phenomenon that cancer cells (which are

epithelial) are found in the white cell layer of whole blood and further teach the morphological identification of the cells.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to extend the methods of '217 to the detection any nucleated cell, including epithelial and cancer cells with a reasonable expectation of success given the knowledge that cancer cells are present in the same layer of the blood as that measured by '217 and one would be motivated to do so in order to detect cancer for clinical implications.

Claims 11 and 12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 5,834,217 as applied to claims 1, 2, 5, 6, 9, 10, 13, and 14 above in view of Wardlaw (U.S. # 4,156,570).

'217 does not specify the use of a microscopical instrument which measures a thickness equal to the focal operating range of 10-100 microns in the claimed method.

Wardlow teaches, however, the use of a microscopical instrument that measures the transverse section of 10-100 microns of the instant tubes to minimize the degree of error. See column 1.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to measure the tubes of '217 using the microscopical analysis of Wardlaw. with a reasonable expectation of success to minimize the degree of error as taught by Wardlaw.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**paula.hutzell@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler

Yvonne Eyler, Ph.D.
Patent Examiner
March 26, 1999